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Rapid Resolution of Necrolytic Migratory Erythema After Glucagonoma Resection

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A 55-year-old man presented with an 11-year history of necrolytic migratory erythema and glossitis. After the patient's serum glucagon was demonstrated to be elevated, computed tomography scan revealed a mass involving the head of the pancreas. The patient underwent a Whipple-type pancreatico-duodenectomy and his rash resolved completely 6 days after tumor resection. He received no adjuvant treatment. A discussion of the varying theories regarding the pathogenesis and treatment of glucagon-associated necrolytic migratory erythema is presented.

KEY WORDS: **pancreas, glucagon, rash**

INTRODUCTION

As early as 1942, Becker et al. [1] described a "diffuse progressive epidermal necrotic rash" associated with some pancreatic neoplasms. In 1966, McGavran et al. [2] reported on an eczematoid, erythematous rash occurring in a patient with a pancreatic neoplasm and elevated serum glucagon. The glucagonoma syndrome was defined by Mallinson et al. in 1977 [3] to include diabetes mellitus, anemia, weight loss, and the distinctive rash referred to as "necrolytic migratory erythema" (NME). Since then, the syndrome has been expanded to include glossitis, hypoaminoacidemia, increased incidence of thromboembolism, and psychiatric disturbances [4].

Several theories have been proposed to explain the characteristic rash seen in patients with a glucagonoma. One theory attributes the NME to hypoaminoacidemia that is frequently observed in patients with a glucagon-secreting tumor. However, some studies report patients whose NME was not affected despite normalization of amino acid levels. In addition, resolution of the rash has been reported in some patients simply from resection of the glucagonoma and normalization of serum glucagon levels [5–8].

We describe a patient with a large, locally resectable glucagon-producing tumor in the head of the pancreas who presented with an 11-year history of severe NME and glossitis. The patient's symptoms resolved completely within 6 days of tumor resection. The rapid resolution of the NME and glossitis associated with normalization of the patient's serum glucagon levels suggests a direct link between the secretory nature of this tumor and the NME.

CASE PRESENTATION

The patient was a 55-year-old white man whose history of present illness began 11 years prior to this admission. At that time he developed a contiguous, macular, intensely red rash over his entire chest and upper abdomen. The rash resolved in 2–3 weeks with cortisone and topical steroids. However, 3 months later he developed a pruritic, erythematous rash over his chest and extremities that responded only transiently to topical steroids. Over the next 10 years, the patient had repeated episodes of a migratory rash that presented at times as macular and erythematous, occasionally as scaly and pruritic, or even as patches of pustules. A biopsy was finally performed and demonstrated NME.

On this admission, the patient denied anorexia, weight loss, abdominal pain, jaundice, or diabetes mellitus. There was no significant family history. The patient's medical history was otherwise insignificant.

On physical examination the patient was noted to have an enlarged, erythematous tongue, and a serpiginous, erythematous rash involving both flanks, upper and lower

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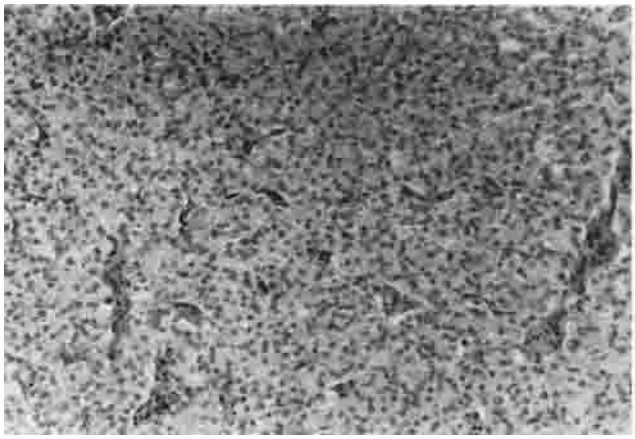

Fig. 1. Representative cross-section of the tumor. Note the uniform sheets of cells, vesicular nuclei, and rare mitotic figures (H&E stain). ×240.

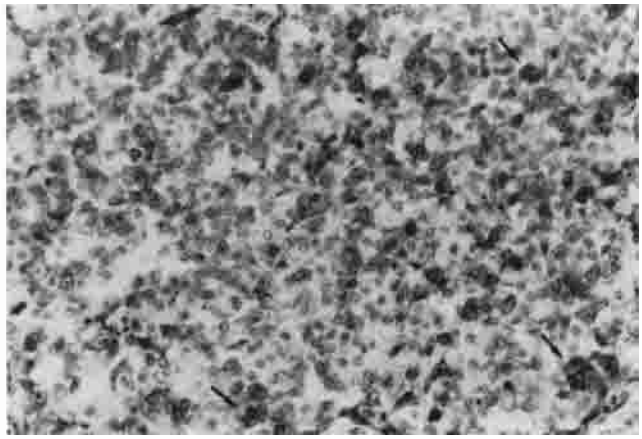

Fig. 2. Immunoperoxidase staining for vasoactive intestinal polypeptide and chromogranin. Note diffuse staining with occasionally intensely staining cells (arrows). ×380.

extremities, back, and perineum. Lesions were noted to vary in severity and stage of resolution. The remainder of the physical examination was unremarkable.

Laboratory values showed hematocrit, glucose, albumin, total protein, alkaline phosphatase, and serum glutamic oxaloacetic transaminase (SGOT) all to be within normal limits. Glucagon level was 2,690 pg/dl (normal <60 pg/dl). Chest roentgenogram, urinalysis, and echocardiogram were all normal. Computed tomography scan showed a 4 cm, well-circumscribed mass in the head of the pancreas. At exploratory laparotomy, the patient had no evidence for metastatic disease and a Whipple-type pancreatico-duodenectomy was performed.

Grossly the tumor was a 4 × 3 × 5 cm soft, multilobulated, yellow mass which appeared to be completely surrounded by pancreatic parenchyma. A portion of the tumor protruded through the ampulla of Vater. Parallel sections through the ampulla revealed that the tumor invaded the submucosa of the duodenum and also involved the pancreatic duct. One peripancreatic lymph node was negative for tumor. On microscopic examination, the tumor consisted of sheets of bland, uniform cells with eosinophilic cytoplasm and vesicular nuclei. Mitotic figures were scarce (Fig. 1). Immunoperoxidase staining for vasoactive intestinal polypeptide and chromogranin was strongly positive, while somatostatin and glucagon stained focally (Figs. 2, 3). Electron microscopy demonstrated neurosecretory granules of the endocrine type.

Serum glucose level on postoperative day 1 was 377 mg/dl. This level stabilized with resumption of oral feedings and the patient did not require insulin on discharge from the hospital. By postoperative day 6, the rash had resolved completely. The serum glucagon level had decreased to 38.9 pg/100 ml on postoperative day 15.

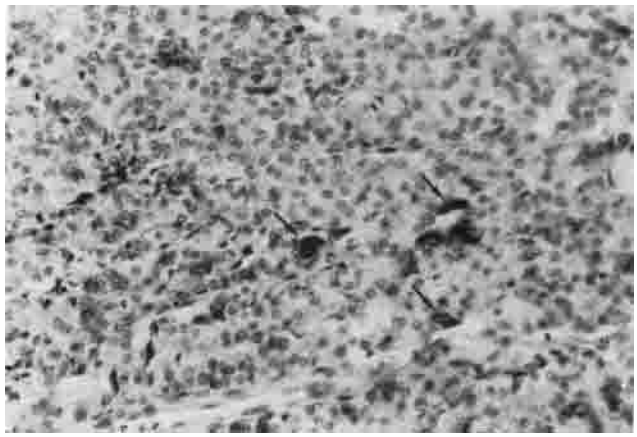

Fig. 3. Immunoperoxidase staining for somatostatin and glucagon. Note the focal areas of increased staining (arrows). ×380.

DISCUSSION

While variable, the clinical signs of the glucagonoma syndrome have been well defined. The classical patient presents with mild diabetes mellitus and a distinctive rash referred to as NME. These patients may also have associated angular stomatitis, glossitis, hypoaminoacidemia, weight loss, anemia, increased venous thrombosis, and psychiatric disturbances. Nevertheless, the rash of NME with elevated serum glucagon level is pathognomonic and may be seen in approximately 70% of patients with the syndrome [8]. It is of note, however, that NME is seen occasionally in patients with other pancreatic cancers, celiac sprue, chronic pancreatitis, hepatic cirrhosis, jejunal adenocarcinoma, and ulcerative colitis [9–11].

There are many theories as to the pathogenesis of NME. One theory suggests that NME results from the hypoaminoacidemia that is observed in many glucagonoma

patients. Shepherd et al. [12] reported relief of NME in a patient treated with intravenous amino acids despite failure with numerous other treatments. Stacpoole [13] proposed that glucagon, acting primarily in the liver, promoted the mobilization of amino acids from body stores. This is thought to occur via glucagon-induced enhancement of hepatic gluconeogenesis. Some authors have suggested that NME results from a systemic deficiency in triglycerides. Delaney and Uff [14] controlled the NME in a patient with a surgically unresectable glucagonoma using omega-3 triglycerides. Blackford et al. [9] also had success using omega-3 triglycerides in conjunction with gamolenic acid to treat a patient with NME who did not have a clinically apparent glucagonoma. Holmes et al. [8] reported dramatic improvement of a patient with an unresectable glucagonoma after administration of somatostatin. This patient's glucagon level decreased, the NME resolved, weight was gained, and neurological symptoms reversed. Finally, Prinz et al. [15] have reported rapid resolution of NME in some patients simply after resection alone.

These data suggest that the cause for the glucagonoma-associated NME is a multifactorial upset in the hormonal-enzyme-substrate dynamic in these patients. As such it seems highly unlikely that pathologic levels of glucagon, amino acids, or triglycerides alone could be responsible. This is consistent with NME being observed in association with other conditions as well. We would suggest that an overall metabolic derangement results in the rash. If the dynamic metabolic milieu is upset by known (measurable) and/or unknown humoral factors being released by a tumor, then both removal of the tumor or manipulation of relevant substrates and enzyme concentrations might restore a more physiologic state, thereby leading to resolution of the rash.

Glucagon is well recognized in having a number of hormonal influences on various tissues throughout the body. Its primary site of action is the liver, where via cyclic-AMP-dependent phosphorylation it increases glycogenolysis, gluconeogenesis, ketogenesis, and lysosome formation. It is also known to decrease glycogenesis, glycolysis, and lipogenesis as well. Its effects on other tissues include increased lipolysis in adipocytes, increased pancreatic section of insulin, and decreased contractility in the gastrointestinal system [16].

Through its actions on varying enzymes, glucagon is vitally important in controlling circulating levels of glucose. Numerous researchers have demonstrated that basal glucagon levels are necessary for maintenance of glucose level, particularly in the postabsorptive phase [17]. Glucagon has been found to be the main regulator of hepatic glucose output, establishing a so-called "set point" [18]. When glucagon is elevated, there is a transient increase in the plasma glucose level (mainly due to glycogenolysis) that wanes after 3–4 hours and then returns to the previous set point [16]. When the liver is chronically exposed to pathologic doses of glucagon, it switches over from a glycogenolytic organ to a gluconeogenic one. This has been demonstrated by measuring the hepatic glucose output from a patient with a glucagonoma concomitant to the hepatic uptake of tagged gluconeogenic precursors. In this patient, the total hepatic output matched the increased uptake [19].

Glucagon has several direct effects on amino acid metabolism. While with normal physiologic doses, glucagon does not seem to affect basal amino acid levels, at pathologic doses (>1,000 pg/dl) glucagon may produce a generalized hypoaminoacidemia [3]. This decrease in circulating amino acids is attributed to the hepatic actions of glucagon (mainly the increased gluconeogenic activity), and the need for substrate. Glucagon is also known to activate the enzymes carbamoyl phosphate synthase and arginosuccinate synthase [16]. Both enzymes are required in the urea cycle and aid in the metabolism of protein by increasing the liver's ability to remove nitrogen. The increased activity of these protein degradation pathways may explain the relationship between hypoaminoacidemia and NME. One current theory of NME suggests that structural proteins of the body, including those in the skin, are harvested to supply the liver with necessary subtrate. Mallinson et al. [3] proposed that the glucagonoma patient with NME has a metabolic state somewhat akin to the starved state. In the starved state, the body attempts to maintain circulating glucose levels. However, patients in the starved state have not been reported to develop NME. It is possible that this can be attributed to the lack of chronicity associated with starvation since the starving body generally fails before an NME-like state arises. This may explain why NME can be found in association with such disease states as chronic pancreatitis, ulcerative colitis, and celiac sprue. These entities may be reviewed as a form of mild, chronic starvation.

In terms of theories of NME being associated with abnormalities in triglyceride metabolism, glucagon is known to decrease triglyceride synthesis by the inhibition of glycerol-3-P-acyl-CoA transferase. Glucagon also inhibits acetyl-CoA carboxylase, which is the primary regulatory step in the synthesis of fatty acids. Thus glucagon may affect the synthesis and packaging of lipids at more than one level [16]. As with the altered metabolism of amino acids, this alteration of lipid metabolism results in a metabolic equilibrium that can be significantly changed simply by the presence or absence of substrate. The chronic elevation of glucagon results in a decreased peripheral and circulating pool of lipids, which might be transiently corrected by supplying triglycerides exogenously. This accounts for the return of NME in successfully treated patients when lipid supplements are subsequently withdrawn [9]. As with protein metabolism, alteration in triglyceride metabolism may play a role in

producing NME in the various disease states mentioned previously.

Understanding the various mechanisms by which glucagon effects normal metabolism shows the rationale behind the numerous treatments used, with varying success, to treat glucagonoma patients. However, if glucagon was the only culprit for NME, then surgical removal or even indirect treatments to decrease glucagon levels (i.e., somatostatin) would work in all patients. Clearly this is not the case, since many patients show no response to such treatment despite no evidence of residual disease. This is further exemplified by many of the above patients who responded to varying treatments with mixed success, and others who required adjuvants to triglyceride treatment [9,14].

In the end, we are still faced with a syndrome and no clear etiology. While we believe this case supports glucagon's key role in NME, one cannot say it is the only player in this syndrome. It is possible that one or more unknown mechanisms or factors may work in concert with and/or independently from glucagon. Until these unknowns are clarified, a standardized effective treatment for glucagon-associated NME will remain an enigma.

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